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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,517	03/16/2004	Xiaoyang Qi	0010872.0529639	4062

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EXAMINER	
SANG, HONG	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
08/28/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/801,517	QI, XIAOYANG	
	Examiner	Art Unit	
	Hong Sang	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *9-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 44-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RE: Qi

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/20/07 has been entered.

2. Claims 1-57 are pending. Claims 9-43 are withdrawn from further consideration as being drawn to non-elected inventions. Claims 1, 2 5, 7, 44, 50, 52, and 56 are amended.

3. Newly submitted claims 3 and 52 comprises species that is distinct from the one originally claimed for the following reasons:

The originally claimed structure analogs of phosphatidylserine is dioleolphosphadylserine (see previous claims 3 and 52). The newly submitted claims 3 and 52 comprises phosphatidic acid, phosphatidylglycerol, phosphatidylinositol, palmitoyloleoylphosphatidylserine, palmitelaidoyloleoylphosphatidylserine, myristoleoyloleoylphosphatidylserine, dilinoleoylphosphatidylserine, palmiticlinoleoylphosphatidylserine, lysophosphatidylserine, and

dioleoylphosphatidylserine. Each of these structure analogs of phosphatidylserine has different structure and different function. Searching them together would impose serious search burden.

Since applicant has received an action on the merits for the originally presented structure analog of phosphatidylserine i.e. dioleoylphosphatidylserine, this species has been constructively elected by original presentation for prosecution on the merits. Accordingly, other structure analogs of phosphatidylserine listed in claim 3 and 52 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. Claims 1-8 and 44-57 are under examination. Due to restriction and species election, claims are examined to the extent that the inner leaflet component is phosphatidylserine, phosphatidylethanolamine, or a structure analog of phosphatidylserine wherein the structure analog of phosphatidylserine is dioleoylphosphatidylserine.

Rejections Withdrawn

5. The rejection of claims 2, 5, and 7 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicant's amendment to the claims.

Response to Arguments

Claim Rejections - 35 USC § 112, 1st paragraph

6. The rejection of claims 1-8 and 50-57 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained.

The response states that applicants have provided sufficient detailed examples in the specification showing peptides comprising less than the full amino acid protein depicted in SEQ ID NO.1 and 2. The US Patent Office clearly does not require a description of every embodiment for peptide claims. It is well known in the art that the proteins of the invention may be altered in various ways including the amino acid substitutions, deletions, truncations, and insertions. Moreover applicants have provided sufficient detail of particular patentable embodiments and a person skilled in the art can easily ascertain the sequences that fall within the scope of the present claims.

Applicant's arguments have been carefully considered but are not found persuasive. The amendment to the claims to recite "having at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO.1/2, wherein the polypeptide comprises a biologically active portion of a (pro)saposin polypeptide comprising at least 25 contiguous amino acids present in a (pro)saposin polypeptide and retain plasma-membrane affinity" does not overcome the instant rejection. As stated in the previous office action, the instant specification may provide an adequate written description of a genus of polypeptide by structurally describing representative homologues, fragment or variants by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, the specification

can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." While the claims have been amended to limit the polypeptide to 95% sequence identity and comprising at least 25 contiguous amino acids, the instant specification does not disclose any fragment of SEQ ID NO.1/2 that has at least 25 amino acids and has the function of retain plasma membrane affinity. The specification does not disclose any polypeptide that is 95% identical to SEQ ID NO.1 and has the function of retain plasma membrane affinity. Furthermore, claims 50-57 recite "a biologically active prosaposin-related polypeptide", which encompass any homologs and variant of prosaposin that are biologically active. No structure feature is recited in these claims. The specification fails to describe the core structure feature that is correlated to the claimed function (retain plasma membrane affinity). Therefore, the specification provides no functional characteristics coupled to structural features. Further, the specification also fails to describe a representative polypeptide that is at least 95% identical to SEQ ID NO. 1 or 2, comprises at least 25 contiguous amino acid and has the function of retain plasma membrane affinity. That is, the specification provides neither a representative number of the claimed polypeptide, nor does it provide a descriptive of structural features that are coupled to the functional features. Thus one of skill in the art would not be able to recognize that applicant was in possession of the invention as now claimed. Therefore, the rejection is deemed proper and maintained.

Claim Rejections - 35 USC § 112, 1st paragraph

7. The rejection of claims 1-8 and 50-57 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an agent comprising an anionic phospholipid, particularly phosphatidylserine and a prosaposin polypeptide of SEQ ID NO.1 or SEQ ID NO.2, does not reasonably provide enablement for an agent comprising any and all inner leaflet component, and any and all prosaposin-related polypeptide of an amino acid sequence that is at least 80% identical to SEQ ID NO.1 or 2 is maintained.

The response states that it is well known in the art that the proteins of the invention may be altered in various ways including the amino acid substitutions, deletions, truncations, and insertions. Moreover applicants have provided sufficient detail of particular patentable embodiments and a person skilled in the art can easily ascertain the sequences that fall within the scope of the present claims.

Applicant's arguments have been carefully considered but are not found persuasive. The amendment to the claims to recite "having at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO.1/2, wherein the polypeptide comprises a biologically active portion of a (pro)saposin polypeptide comprising at least 25 contiguous amino acids present in a (pro)saposin polypeptide and retain plasma-membrane affinity" does not overcome the instant rejection. Because applicant fails to provide adequate written description for the claimed peptide (see above), particularly because the instant specification does not disclose the core structure that is correlated to the functional feature, given the unpredictability of the protein chemistry, one skilled

in the art would not know how to modify the SEQ ID NO.1 or 2 to obtain the polypeptide that is at least 95% identical to SEQ ID NO. 1 or 2, comprises 25 amino acids, and most importantly possess the required function i.e. retain plasma-membrane affinity. Furthermore, claims 50-57 recite "a biologically active prosaposin-related polypeptide", which encompass any homologs and variant of prosaposin that are biologically active. No structure feature is recited in these claims. The specification does not provide any guidance on how to make such broad class of polypeptide that has the claimed function. Because of these reasons the rejection is deemed proper and maintained.

Double Patenting

8. The rejection of claims 1-3, 44-47 and 50-52 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 16, 17, 21 and 22 of U.S. Patent No. 6,872,406 in view of Vaccaro et al. (FEBS Lett. 1994, 349: 181-186, IDS) is maintained.

The response states a Terminal Disclaimer will be filed if conflicting claims are issued.

Since no Terminal Disclaimer has been filed, the rejection is maintained.

Double Patenting

9. The provisional rejection of claims 1-3, 44-47 and new claims 50-52 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over

claims 16, 17, 21 and 22 of copending Application No. 10/967,921 in view of Vaccaro et al. (FEBS Lett. 1994, 349: 181-186, IDS) is maintained.

The response states a Terminal Disclaimer will be filed if conflicting claims are issued.

Since no Terminal Disclaimer has been filed, the rejection is maintained.

Claim Rejections - 35 USC § 103

10. The rejection of claims 1-8, and 44-57 under 35 U.S.C. 103(a) as being unpatentable over Vaccaro et al. (FEBS 1993, 336(1): 159-162) in view of the teachings of O'brien et al. (WO9503821A1), as evidenced by Vaccaro et al. (FEBS, 1994, 349: 181-186, IDS) is maintained.

The response states that the teachings of Vaccaro and O'Brien show forming liposomal vesicles and then adding saposin C to the formulation, resulting in a surface interaction of the protein with the vesicles. A lipid/saposin vesicle formed by this method will not function the same and will not exhibit anti-tumor activity as with the vesicles of the present invention. The claims are also amended to clarify this important feature showing that the prosaposin related polypeptide and the inner leaflet component are combined in an acidic buffer and then treated together to form a nanovesicle exhibiting anti-tumor activity.

Applicant's arguments have been carefully considered but are not persuasive. The claims as amended recite " wherein the prosaposin related polypeptide and the inner leaflet component are contacted with an acidic buffer and treated together to form

a nanovesicle exhibiting anti-tumor activity". Vaccaro (1993) teaches mixing Sap C, and different amount of PS vesicles in 10 mM acetate buffer (pH 5.4) and incubating at 37°C for 30 min (see page 160, left column, section 2.5). The PS vesicles are small unilamellar vesicles (SUV) or large unilamellar vesicles (LUV) (see page 160, left column, section 2.7). Therefore, Vaccaro (1993) teaches the new limitation "contacting PS and Saposin C with an acidic buffer and treated together to form a nanovesicle". In Vaccaro (1993), the Sap C and lipid vesicle are mixed in an acidic buffer and treated at 37°C for 30 min, the resulting nanovesicle would have the anti-tumor activity. Moreover, the instant specification does not teach that only the nanovesicle form of PS/Sap C has antitumor activity (see specification, page 21, paragraph [0071]). For example, in Working Examples, the PS together with Sap C that are not in nanovesicle form show antitumor activity.

New Grounds of Objections and Rejections

Claim Objections

11. Claim 50 is objected to because of the following informalities: Claim 50 has a typographical error. The word "rcontacted" on line 5 should spell "contacted". Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

12 The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 44-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 recites the limitation "the prosaposin related polypeptide and the inner leaflet component" on line 5. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112, 1st paragraph

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-9, and 44-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **New Matter** rejection.

The term "are contacted with an acidic buffer" recited in claims 1, 44, and 50 is considered new matter since the specification, drawings and claims as filed disclose only "McIlvanine buffer (pH 4.7)". There is no clear support for "acidic buffer". The term "acidic buffer" changes the scope of the invention as originally disclosed. The invention as originally filed disclose one specific acidic buffer i.e. McIlvanine buffer. By using the term "acidic buffer", applicants are claiming any and all acidic buffers.

If applicant believes that support for the above-mentioned phrases or terms is present in the specification, claims or drawing as originally filed, applicant must, in responding to this action, point out with particularity, where such support may be found.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1-8, and 44-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vaccaro et al. (FEBS 1993, 336(1): 159-162) in view of the teachings of O'brien et al. (WO9503821A1), Vaccaro et al. (FEBS, 1994, 349: 181-186, IDS), and Egas et al. (J. Biol. Chem. 2000, 275(49): 38190-38196).

The teachings of Vaccaro et al. (1993), O'brien and Vaccaro (1993) have been set forth before as they apply to claims 1-8 and 44-57 (see previous office action).

Vaccaro (1993) and O'brien do not teach the lipid is phosphatidylethanolamine. However, these deficiencies are made up for in the teachings of Vaccaro et al. (1994) and Egas et al.

Vaccaro (1994) teaches mixing Sap C, and PS (phosphatidylserine) vesicles in 10 mM acetate buffer (pH 4.5-6.0) and incubating at 37°C for 30 min (see page 182, left column, section 2.5). The PS vesicles are small unilamellar vesicles (SUV) or large

unilamellar vesicles (LUV) (see page 182, left column, section 2.4). Vaccaro (1994) teaches that Sap C induces leakage of PS containing liposome at low pH (see page 182, left column, section 2.7, and page183). Vaccaro (1994) teaches adding Sap C to the liposome (LUV and SUV vesicles) that contain both N-NBD-PE and N-Rh-PE at acidic condition (see page 182, section 2.6 and 3.1).

Egas et al. teach that the saposin-like domain of the plant aspartic proteinase precursor induces leakage of both PA/PE and PA/PE/PS (phosphatidic acid/phosphatidylethanolamine/phosphatidylserine) vesicles at low pH (see page 38192, right column, last paragraph). Egas et al. teach that this effect was dependent on phospholipid composition, with higher leakage activity in the presence of PA/PE/PS vesicles.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the assay of Vaccaro (1993) to study the effect of Sap C in combination of different phospholipids, such as PA/PE/PS, on the stimulation of glucosylceramidase activity in view of the teachings of Vaccaro (1994) and Egas et al. One would have been motivated to do so because Vaccaro teaches that Sap C induces leakage of a vesicle comprising both PS and PE, and Egas teaches that the effect of Saposin domain-like peptide on the leakage of phospholipid vesicle depends on the phospholipid composition, with higher effect in the presence of PA/PE/PS vesicles. As such one skilled in the art would expect that PA/PE/PS vesicles when combined with Sap C would be more active than PS alone on the stimulation of glucosylceramidase activity. Moreover, it is known in the art that Saposins and

prosaposin bind to different phospholipids not just PS, therefore one skilled in the art would have been motivated to study the interaction of saposins or prosaposin with other phospholipids. Because PE is one of the main phospholipids found in cell membrane, and like PS, is also located in inner leaflet of membrane, it would have been obvious to one skilled in the art to study the interaction of PE and saposins or prosaposin. Moreover, one of ordinary skill in the art would have a reasonable expectation of success to modify the assay of Vaccaro (1993) to use vesicle comprising PE such as PA/PE/PS to study the effect of Sap C on the stimulation of glucosylceramidase activity because Vaccaro (1993) teaches the method, Vaccaro (1994) and Egas et al. teach how to make vesicles comprising PS and PE.

Conclusion

18. No claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Hong Sang, Ph.D.
Art Unit: 1643
8/2/2007

/Christopher Yaen/
Primary Examiner
Art Unit 1643
August 16, 2007